Gender Differences and NPS

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Contributor: Liana Fattore , Matteo Marti , Rafaela Mostallino , Maria Paola Castelli

Sex and gender deeply affect the subjective effects and the pharmaco-toxicological responses to drugs. Men are more likely than women to use almost all types of illicit drugs and to present to emergency departments for serious or fatal intoxications. However, women are just as likely as men to develop substance use disorders, and may be more susceptible to craving and relapse.

Gender/sex differences novel psychoactive substances male/female differences in response to drugs

Men and women differ in terms of physiology and pathophysiology. Male/female differences are important in medicine, and can be responsible for sex-specific clinical manifestations and response to therapies. Sex differences in bioavailability, distribution, metabolism and eliminations of drugs can affect their efficacy and safety and some drugs may be more effective in women than in men, or vice versa[1]. Sex-related differences have been demonstrated for many drugs[2][3][4], including drugs of abuse[5]. Clinical and preclinical studies provided compelling evidence of hormonal- and sex-dependent differences in the wanted and unwanted effects of recreational drugs[6][7][8][9] and in drug sensitivity[10], which may result in a different likelihood of seeking and taking drugs on future occasions and in a different proneness to develop dependence[11]. Socially gendered factors (e.g., social stigma) may also interact with biological factors in modulating drug consumption and the efficacy of therapeutic interventions[12]. According to the last World Drug Report (WDR 2020), drug use is more prevalent among males than females; yet, women are more affected than men by the non-medical use of sedatives and tranquillizers, and substance use disorders are more prevalent in female than in male prisoners[13].

Over the last decade, an incredibly high number of novel psychoactive substances (NPS) have emerged as alternatives to regulated drugs, and new ones are continuously appearing on the internet, social networks and smartphone apps at an incredibly high rate[14]. The NPS market is diverse and dynamic, with the number of NPS rising from 166 by the end of 2009 to 950 substances detected by the end of 2019[13]. These new drugs are not subjected to clinical trials and information concerning toxicity and specific associated effects is still limited. Yet, animal and human studies showed that NPS are able to elicit not only rewarding and reinforcing effects [15][16][17][18], but also toxic effects of varying severity, at both the peripheral and central levels[19][20], despite an apparent, hazardous perception of safety[21]. Most of them are synthetic cannabinoids and cathinones, new hallucinogen and dissociative drugs or synthetic opioids, these latter representing a major source of social and clinical alarm, due to the numerous fatalities and intoxications associated with their use[22]. NPS represent a growing concern especially for mental health services[23][24], as they have been associated with the risk of violence in patients presenting to acute mental health services[25][26].

The use of NPS is widespread among adolescents, and a nationally representative study enrolling students in 8th to 12th grades across the US showed that boys are at greater risk for using synthetic cannabinoids and synthetic cathinones than girls[27]. Notably, NPS use is increasing in both male and female treatment-seeking opiate-dependent patients as a replacement to heroin and other opiates[28], due mostly to practical (e.g., greater availability) and economic rather than pharmacological factors[29]. There is also the possibility that female users may be at risk for being the experimental subjects of immoral drug dealers, i.e., to probe the effects of unknown, experimental synthetic drugs[30].

To date, knowledge of potential sex-dependent effects in the use and abuse of NPS is very scarce. Unfortunately, in many human and clinical studies involving subjects of both sexes, authors did not directly compare females to males, leaving the possibility of the existence of significant sex (animal studies) and gender (clinical studies) differences an open question.

The existence of a (still limited) number of differences in the behavioral and pharmaco-toxicological responses induced by NPS in male and female subjects. In general, the use of most NPS is prevalent among men than women. Preclinical studies, however, which allow greater control of individual variability (health status, taking other drugs, emotional conditions), have shown that females are more sensitive to the rewarding effects of synthetic cannabinoids and to the anxiety-related effects of synthetic cathinones than males (Table 1). Current knowledge on sex and gender differences in NPS-induced effects is still inadequate, but the need for more studies is supported by the compelling evidence, showing important sex differences in the effects of their referent drugs (e.g., THC, cocaine, amphetamine, morphine). Similar to studies required for monitoring the pharmacological effects of therapeutic drugs, preclinical studies and clinical evaluations are needed to better understand the pharmaco-toxicological effects that NPS cause as a function of sex and gender. Such knowledge, in turn, will allow more effective, sex-tailored interventions to manage acute intoxications and reduce drug use.

Table 1. Summary of the evidence available so far describing sex-dependent differences or similarities in the prevalence of use and effects induced by new psychoactive substances (NPS) in males (M) and females (F). The symbol ? indicates the lack of data specifically comparing M vs. F. Abbreviations: 25I-NBOMe: dimethoxy-*N*-(2-methoxybenzyl)phenethylamine; α-PVP: α-pyrrolidinopentiophenone; CPP: conditioned place preference; DD: drug discrimination; IVSA: intravenous self-administration; KET: ketamine; MDPV: methylenedioxypyrovalerone; PPI: pre-pulse inhibition.

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	Scras	Synthetic Cathinones	Phenethylamines	Opioids
Prevalence of use (%)	M > F[31]	M > F [32][33][34] M = F[35] (mephedrone)	M > F [36][37][38][39][40][1][41][42]	M > F [43][44] F > M [45][46] (prescribed drugs)
Intoxications (%)	M > F [31]	M > F [47]	?	M > F[43][44]
Polydrug use	M > F [48][49][50][51][52] (nicotine, alcohol, marijuana)	M > F [32][33] (alcohol, opioids)	?	?
Age of 1st use	M > F [53]	?	?	?
Sensitivity to adverse effects	M > F [54] (general side effects) F > M [55] (agitation, psychosis)	F > M [56] (anxiety, rats) M > F [57] (cardiovascular effects, rats) F > M[58] (tolerance to drug-induced hyperthermia, rats)	F > M [41] (2C-B, emotional verbal fluency) M > F [41] (2C-B, reduction in tiredness) F > M [42] (25I-NBOMe, hyperthermia) M > F [42] (25I-NBOMe, analgesia) M = F [42] (25I-NBOMe, PPI and visual sensorimotor responses)	?
Sensitivity to rewarding effects (animals)	F > M [59][60][61][62] (IVSA and DD)	M = F [63][64] (MDPV CPP and α-PVP IVSA) M > F [65] (α-PVP CPP)	?	F > M[66] (IVSA) M > F [[67] (food choice procedure)

References

1. Farkouh, A.; Riedl, T.; Gottardi, R.; Czejka, M.; Kautzky-Willer, A. Sex-Related differences in pharmacokinetics and pharmacodynamics of frequently prescribed drugs: A review of the literature. Adv. Ther. 2020, 37, 644–655.
2. Harris, R.Z.; Benet, L.Z.; Schwartz, J.B. Gender effects in pharmacokinetics and pharmacodynamics. Drugs 1995, 50, 222–239.

3. Tanaka, E. Gender-related differences in pharmacokinetics and their clinical significance. J. Clin. Pharm. Ther. 1999, 24, 339–346.
4. Xie, C.X.; Piecoro, L.T.; Wermeling, D.P. Gender-related considerations in clinical pharmacology and drug therapeutics. Crit. Care Nurs. Clin. N. Am. 1997, 9, 459–468.
5. Fattore, L.; Altea, S.; Fratta, W. Sex differences in drug addiction: A review of animal and human studies. Womens Health 2008, 4, 51–65.
6. Fattore, L.; Fratta, W. How important are sex differences in cannabinoid action? Br. J. Pharmacol. 2010, 160, 544–548.
7. Mendrek, A.; Fattore, L. Sex differences in drug-induced psychosis. Curr. Opin. Behav. Sci. 2016, 13, 152–157.
8. Agabio, R.; Campesi, I.; Pisanu, C.; Gessa, G.L.; Franconi, F. Sex differences in substance use disorders: Focus on side effects. Addict. Biol. 2016, 21, 1030–1042.
9. Agabio, R.; Pisanu, C.; Gessa, G.L.; Franconi, F. Sex differences in alcohol use disorder. Curr. Med. Chem. 2017, 24, 2661–2670.
10. Struik, D.; Sanna, F.; Fattore, L. The Modulating Role of Sex and Anabolic-Androgenic Steroid Hormones in Cannabinoid Sensitivity. Front. Behav. Neurosci. 2018, 12, 249.
11. Fattore, L. Reward processing and drug addiction: Does sex matter? Front. Neurosci. 2015, 9, 329.
12. Becker, J.B.; McClellan, M.; Reed, B.G. Sociocultural context for sex differences in addiction. Addict. Biol. 2016, 21, 1052–1059.
13. United Nations. World Drug Report 2020; Sales No. E.20.XI.6; United Nations Office on Drugs and Crime: Vienna, Austria, 2020.
14. Miliano, C.; Margiani, G.; Fattore, L.; De Luca, M.A. Sales and Advertising Channels of New Psychoactive Substances (NPS): Internet, Social Networks, and Smartphone Apps. Brain Sci. 2018, 8, 123.
15. Miliano, C.; Serpelloni, G.; Rimondo, C.; Mereu, M.; Marti, M.; De Luca, M.A. Neuropharmacology of New Psychoactive Substances (NPS): Focus on the rewarding and reinforcing properties of cannabimimetics and amphetamine-like stimulants. Front. Neurosci. 2016, 10, 153.
16. Zanda, M.T.; Fadda, P.; Chiamulera, C.; Fratta, W.; Fattore, L. Methoxetamine, a novel psychoactive substance with important pharmacological effects: A review of case reports and preclinical findings. Behav. Pharmacol. 2016, 27, 489–496.
17. Zanda, M.T.; Fadda, P.; Antinori, S.; Di Chio, M.; Fratta, W.; Chiamulera, C.; Fattore, L. Methoxetamine affects brain processing involved in emotional response in rats. Br. J. Pharmacol.

2017, 174, 3333–3345.

18. Bilel, S.; Tirri, M.; Arfè, R.; Stopponi, S.; Soverchia, L.; Ciccocioppo, R.; Frisoni, P.; Strano-Rossi, S.; Miliano, C.; De-Giorgio, F.; et al. Pharmacological and behavioral effects of the synthetic cannabinoid AKB48 in rats. Front. Neurosci. 2019, 13, 1163.
19. Bilel, S.; Tirri, M.; Arfè, R.; Ossato, A.; Trapella, C.; Serpelloni, G.; Neri, M.; Fattore, L.; Marti, M. Novel halogenated synthetic cannabinoids impair sensorimotor functions in mice. Neurotoxicology. 2020, 76, 17–32.
20. Costa, G.; De Luca, M.A.; Piras, G.; Marongiu, J.; Fattore, L.; Simola, N. Neuronal and peripheral damages induced by synthetic psychoactive substances: An update of recent findings from human and animal studies. Neural Regen. Res. 2020, 15, 802–816.
21. De-Giorgio, F.; Bilel, S.; Tirri, M.; Arfè, R.; Trapella, C.; Camuto, C.; Foti, F.; Frisoni, P.; Neri, M.; Botrè, F.; et al. Methiopropamine and its acute behavioral effects in mice: Is there a gray zone in new psychoactive substances users? Int. J. Legal Med. 2020, 134, 1695–1711.
22. Frisoni, P.; Bacchio, E.; Bilel, S.; Talarico, A.; Gaudio, R.M.; Barbieri, M.; Neri, M.; Marti, M. Novel synthetic opioids: The pathologist’s point of view. Brain Sci. 2018, 8, 170.
23. Martinotti, G.; Corazza, O.; Achab, S.; Demetrovics, Z. Novel psychoactive substances and behavioral addictions. Biomed. Res. Int. 2014, 2014, 534523.
24. Orsolini, L.; Chiappini, S.; Papanti, D.; De Berardis, D.; Corkery, J.M.; Schifano, F. The Bridge Between Classical and “Synthetic”/Chemical Psychoses: Towards a Clinical, Psychopathological, and Therapeutic Perspective. Front. Psychiatry 2019, 10, 851.
25. Shafi, A.; Gallagher, P.; Stewart, N.; Martinotti, G.; Corazza, O. The risk of violence associated with novel psychoactive substance misuse in patients presenting to acute mental health services. Hum. Psychopharmacol. Clin. Exp. 2017, 32, e2606.
26. Bonaccorso, S.; Metastasio, A.; Ricciardi, A.; Stewart, N.; Jamal, L.; Rujully, N.U.D.; Theleritis, C.; Ferracuti, S.; Ducci, G.; Schifano, F. Synthetic Cannabinoid use in a Case Series of Patients with Psychosis Presenting to Acute Psychiatric Settings: Clinical Presentation and Management Issues. Brain Sci. 2018, 8, 133.
27. Patrick, M.E.; O’alley, P.M.; Kloska, D.D.; Schulenberg, J.E.; Johnston, L.D.; Miech, R.A.; Bachman, J.G. Novel psychoactive substance use by US adolescents: Characteristics associated with use of synthetic cannabinoids and synthetic ca thinones. Drug Alcohol Rev. 2016, 35, 586–590.
28. Heikman, P.; Sundström, M.; Pelander, A.; Ojanperä, I. New psychoactive substances as part of polydrug abuse within opioid maintenance treatment revealed by comprehensive high-resolution mass spectrometric urine drug screening. Hum. Psychopharmacol. 2016, 31, 44–52.

29. Kapitány-Fövény, M.; Farkas, J.; Pataki, P.A.; Kiss, A.; Horváth, J.; Urbán, R.; Demetrovics, Z. Novel psychoactive substance use among treatment-seeking opiate users: The role of life events and psychiatric symptoms. Hum. Psychopharmacol. 2017, 32, e2602.
30. Caloro, M.; Calabrò, G.; Kotzalidis, G.D.; Cuomo, I.; Corkery, J.M.; Vento, A.M.; Lionetto, L.; De Filippis, S.; Ranieri, V.; Lonati, D.; et al. Use of benzylglycinamide by a HIV-seropositive polysubstance user: The changing pattern of novel psychoactive substance use among youths. Addict. Behav. 2016, 60, 53–57.
31. Becker, J.B.; Hu, M. Sex differences in drug abuse. Front. Neuroendocrinol. 2008, 29, 36–47.
32. Bernstein, D.L.; Nayak, S.U.; Oliver, C.F.; Rawls, S.M.; Rom, S. Methylenedioxypyrovalerone (MDPV) impairs working memory and alters patterns of dopamine signaling in mesocorticolimbic substrates. Neurosci. Res. 2020, 155, 56–62.
33. Schiavi, S.; Melancia, F.; Carbone, E.; Buzzelli, V.; Manduca, A.; Jiménez Peinado, P.; Zwergel, C.; Mai, A.; Campolongo, P.; Vanderschuren, L.J.M.J.; et al. Detrimental effects of the ‘bath salt’ methylenedioxypyrovalerone on social play behavior in male rats. Neuropsychopharmacology 2020.
34. Lopez-Rodriguez, A.B.; Viveros, M.P. Bath salts and polyconsumption: In search of drug-drug interactions. Psychopharmacology 2019, 236, 1001–1014.
35. Winstock, A.; Mitcheson, L.; Ramsey, J.; Davies, S.; Puchnarewicz, M.; Marsden, J. Mephedrone: Use, subjective effects and health risks. Addiction 2011, 106, 1991–1996.
36. Sanders, B.; Lankenau, S.E.; Bloom, J.J.; Hathazi, D. “Research chemicals”: Tryptamine and phenethylamine use among high-risk youth. Subst. Use Misuse 2008, 43, 389–402.
37. González, D.; Torrens, M.; Farré, M. Acute Effects of the Novel Psychoactive Drug 2C-B on Emotions. Biomed Res. Int. 2015, 2015, 643878.
38. Herian, M.; Wojtas, A.; Kamińska, K.; Świt, P.; Wach, A.; Gołembiowska, K. Hallucinogen-Like Action of the Novel Designer Drug 25I-NBOMe and Its Effect on Cortical Neurotransmitters in Rats. Neurotox. Res. 2019, 36, 91–100.
39. Lawn, W.; Barratt, M.; Williams, M.; Horne, A.; Winstock, A. The NBOMe hallucinogenic drug series: Patterns of use, characteristics of users and self-reported effects in a large international sample. J. Psychopharmacol. 2014, 28, 780–788.
40. Forrester, M.B. NBOMe designer drug exposures reported to Texas poison centers. J. Addict. Dis. 2014, 33, 196–201.
41. Larson, E.B.; Carroll, M.E. Estrogen receptor beta, but not alpha, mediates estrogen’s effect on cocaine-induced reinstatement of extinguished cocaine-seeking behavior in ovariectomized female rats. Neuropsychopharmacology 2007, 32, 1334–1345.

42. Srisuma, S.; Bronstein, A.C.; Hoyte, C.O. NBOMe and 2C substitute phenylethylamine exposures reported to the National Poison Data System. Toxicol. (Phila) 2015, 53, 624–628.
43. Coopman, V.; Blanckaert, P.; Van Parys, G.; Van Calenbergh, S.; Cordonnier, J. A case of acute intoxication due to combined use of fentanyl and 3,4-dichloro-N-[2-(dimethylamino) cyclohexyl]-N-methylbenzamide (U-47700). Forensic Sci. Int. 2016, 266, 68–72.
44. Domanski, K.; Kleinschmidt, K.C.; Schulte, J.M.; Fleming, S.; Frazee, C.; Menendez, A.; Tavakoli, K. Two cases of intoxication with new synthetic opioid, U-47700. Clin. Toxicol. (Phila) 2017, 55, 46–50.
45. Wang, J.B.; Johnson, P.S.; Persico, A.M.; Hawkins, A.L.; Griffin, C.A.; Uhl, G.R. Human mu opiate receptor. cDNA and genomic clones, pharmacologic characterization and chromosomal assignment. FEBS Lett. 1994, 338, 217–222.
46. Cox, B.M. Pharmacology of opioid drugs. In The Opiate Receptors; Pasternak, G.W., Ed.; Springer: New York, NY, USA, 2011; pp. 23–57.
47. Greaves, L.; Hemsing, N. Sex and Gender Interactions on the Use and Impact of Recreational Cannabis. Int. J. Environ. Res. Public Health. 2020, 17, 509.
48. Vandrey, R.; Dunn, K.E.; Fry, J.A.; Girling, E.R. A survey study to characterize use of Spice products (synthetic cannabinoids). Drug Alcohol Depend. 2012, 120, 238–241.
49. Castellanos, D.; Singh, S.; Thornton, G.; Avila, M.; Moreno, A. Synthetic cannabinoid use: A case series of adolescents. J. Adolesc. Health 2011, 49, 347–349.
50. Forrester, M.B.; Kleinschmidt, K.; Schwarz, E.; Young, A. Synthetic cannabinoid exposures reported to Texas poison centers. J. Addict. Dis. 2011, 30, 351–358.
51. Gunderson, E.W.; Haughey, H.M.; Ait-Daoud, N.; Joshi, A.S.; Hart, C.L. A survey of synthetic cannabinoid consumption by current cannabis users. Subst. Abus. 2014, 35, 184–189.
52. Hu, X.; Primack, B.A.; Barnett, T.E.; Cook, R.L. College students and use of K2: An emerging drug of abuse in young persons. Subst. Abus. Treat. Prev. Policy 2011, 6, 16.
53. Gutierrez, K.M.; Cooper, T.V. Investigating correlates of synthetic marijuana and Salvia use in light and intermittent smokers and college students in a predominantly Hispanic sample. Clin. Psychopharmacol. 2014, 22, 524–529.
54. Egan, K.L.; Suerken, C.K.; Reboussin, B.A.; Spangler, J.; Wagoner, K.G.; Sutfin, E.L.; Debinski, B.; Wolfson, M. K2 and spice use among a cohort of college students in southeast region of the USA. Am. J. Drug Alcohol Abuse 2015, 41, 317–322.
55. Vidourek, R.A.; King, K.A.; Burbage, M.L. Reasons for synthetic THC use among college students. J. Drug Educ. 2013, 43, 353–363.

56. Jones, L.; Reed, P.; Parrott, A. Mephedrone and 3,4-methylenedioxy-methamphetamine: Comparative psychobiological effects as reported by recreational polydrug users. Psychopharmacol. 2016, 30, 1313–1320.
57. Daniel, J.J.; Hughes, R.N. Increased anxiety and impaired spatial memory in young adult rats following adolescent exposure to methylone. Biochem. Behav. 2016, 146–147, 44–49.
58. Nelson, K.H.; Manke, H.N.; Imanalieva, A.; Rice, K.C.; Riley, A.L. Sex differences in α-pyrrolidinopentiophenone (α-PVP)-induced taste avoidance, place preference, hyperthermia and locomotor activity in rats. Biochem. Behav. 2019, 185, 172762.
59. Tait, R.J.; Caldicott, D.; Mountain, D.; Hill, S.L.; Lenton, S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin. Toxicol. (Phila) 2016, 54, 1–13.
60. The DAWN Report: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids; Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality: Rockville, MD, USA, 2012.
61. Gatch, M.B.; Forster, M.J. Delta9-Tetrahydrocannabinol-like discriminative stimulus effects of compounds commonly found in K2/Spice. Pharmacol. 2014, 25, 750–757.
62. Järbe, T.U.; McMillan, D.E. Delta 9-THC as a discriminative stimulus in rats and pigeons: Generalization to THC metabolites and SP-111. Psychopharmacology 1980, 71, 281–289.
63. Milesi-Hallé, A.; McMillan, D.E.; Laurenzana, E.M.; Byrnes-Blake, K.A.; Owens, S.M. Sex differences in (+)-amphetamine- and (+)-methamphetamine-induced behavioral response in male and female Sprague–Dawley rats. Biochem. Behav. 2007, 86, 140–149.
64. Alsufyani, H.A.; Docherty, J.R. Gender differences in the effects of cathinone and the interaction with caffeine on temperature and locomotor activity in the rat. J. Pharmacol. 2017, 809, 203–208.
65. McClenahan, S.J.; Hambuchen, M.D.; Simecka, C.M.; Gunnell, M.G.; Berquist, M.D.; Owens, S.M. Cardiovascular effects of 3,4-methylenedioxypyrovalerone (MDPV) in male and female Sprague-Dawley rats. Drug Alcohol Depend. 2019, 195, 140–147.
66. Brigitte L. Kieffer; Opioids: first lessons from knockout mice. *Trends in Pharmacological Sciences* **1999**, *20*, 19-26, 10.1016/s0165-6147(98)01279-6.
67. Selley, D.E.; Liu, Q.; Childers, S.R. Signal transduction correlates of mu opioid agonist intrinsic efficacy: Receptor-stimulated [35S]GTP gamma S binding in mMOR-CHO cells and rat thalamus. J. Pharmacol. Exp. Ther. 1998, 285, 496–505.